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Clobazam in partial status epilepticus

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Clobazam is the first and only 1,5-benzodiazepine to be used in the management of epilepsy. The use and effectiveness of oral clobazam in patients with status epilepticus has only been previously described in one study of 16 cases, seven of whom were in complex partial status. We have used clobazam in four patients with EEG-proven partial status epilepticus refractory to standard antiepileptic drugs. In all cases, except one, the seizure activity was controlled within 2 hr of administering clobazam. Our four patients responded promptly to an oral loading of clobazam which was approximately twice the usual daily maintenance dose. The drug was well tolerated and no adverse effects were seen. Clobazam's effectiveness as a first-line agent remains to be studied. Further controlled studies are recommended.

Key words: clobazam; partial status epilepticus; status epilepticus; anticonvulsant.

INTRODUCTION

Clobazam is the first and only 1,5-benzodiazepine to be used in the management of epilepsy[1]. It differs from other antiepileptic benzodiazepines in that its nitrogen radicals are located in positions 1 and 5 rather than 1 and 4[2]. Like all other benzodiazepines, clobazam acts through the benzodiazepine receptors on the gamma-aminobutyric acid (GABA) receptor complex.

Clobazam is rapidly and almost completely absorbed (87%) with peak plasma levels achieved within 1 to 4 hr[3]. The drug is relatively insoluble and is therefore not available for intravenous or intramuscular use[1]. This drug is extensively metabolized to N-desmethylclobazam which contributes significantly to clobazam's antiepileptic activity[4].

In experimental models as well as in humans, clobazam has been shown to be an effective broad spectrum antiepileptic agent against partial and generalized seizures which is more effective after oral administration than other benzodiazepines[1].

The use and effectiveness of oral clobazam in patient with status epilepticus has only been previously described in one study of 16 cases, seven of whom were in complex partial status[5]. We have used clobazam in 4 patients with EEG-proven partial status epilepticus refractory to standard medication. In all cases, except one, the seizure activity was controlled within 2 hr of administering clobazam.

CASE 1

A 46-year-old right-handed man presented with a 4-week history of episodic 'confusion'. These episodes had a sudden onset, lasted less than 1 min and occurred several times per hour. During these events he would stop talking and would have no recollection of this. The day before admission he had suffered a brief episode of loss of consciousness. Since then, he had been awake but withdrawn. No abnormal movements were observed. His past medical history was positive for alcohol abuse, seizure disorder (asymptomatic for 4 years and off medication for 2 years) and he was HIV positive for the past 6 years. The physical examination disclosed a thin man in no acute distress, afebrile with normal vital signs. The neurological exam showed an alert patient disoriented to place and person, with no speech difficulty. His memory was severely impaired. He could not do serial sevens and was not able to repeat 3 words after 3 min. During the examination he had several episodes where his eyes would open and stare, he would not be able to continue the conversation and would only say he was having 'a spell'. In between he was withdrawn,

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but would answer questions and follow commands. At times he looked towards the right. No abnormal movements were noted. Blood biochemistry, ECG and chest x-ray were normal. CT scan of the head showed mild cortical atrophy. The CSF examination was normal including gram stain, cultures and India Ink preparation. EEG showed build-up of right frontotemporal rhythmic theta activity during the seizures which recurred every few min (Fig. 1a and b). During that time the patient was unresponsive and showed some automatisms.

The patient was treated with phenytoin 18 mg/kg IV and lorazepam 4 mg IV. Despite treatment the seizure activity continued for 12 hr but responded completely within 1 hr of a single oral dose of clobazam 70 mg. EEG 3 hr after the dose revealed no seizure activity. Serum phenytoin level measured 2-hr after the bolus was 68 μmol/L and serum clobazam level was 4.1 μmol/L.

CASE 2

A 30-year-old left-handed woman started to experience persistent uncontrolled contractions in her right biceps on the night prior to admission. There was no spread of the movement into neck, face or right leg. She did not experience loss of consciousness, bowel or bladder incontinence. She had a long pasthistory of epilepsy, with generalized seizures from the age of 6 years. Since then she had continued to experience periodic focal motor seizures of the right arm. Medication on admission were carbamazepine 1000 mg/day, phenytoin 150 mg/day and clonazepam 6 mg/day. Physical examination showed an alert and very anxious woman distressed over her uncontrollable arm movements. She was afebrile, BP 100/70, HR 70 and RR 16. Neurological examination showed her to be oriented in all spheres and cooperative. Examination of the extremities disclosed that her right hand was smaller than her left and there were repetitive clonic contractions of the right biceps. Movement, power and tone were normal. Deep tendon reflexes were increased in the right arm. Blood biochemistry, ECG and chest x-ray were normal. Drug levels on admission were: phenytoin 41 μmol/L and carbamazepine 26 μmol/L. EEG showed frequent left fronto-central spikes which were accompanied by twitching movements of the right biceps muscle (Fig. 2).

The patient received additional phenytoin IV and several doses of lorazepam 1 mg IV. Despite the treatment the seizure activity persisted for 10 hr. She was then loaded with 60 mg of clobazam orally and her seizure activity resolved completely in 2 hr. Serum clobazam measured 2 hr after the dose was 2.1 μmol/L.

CASE 3

A 71-year-old right-handed woman was admitted, after having an episode of seizures and being acutely confused. She had a past medical history of chronic obstructive pulmonary disease, a right frontal infarct and was doing well until a few days prior to admission when she developed an upper respiratory tract infection with fever and diarrhoea. On the morning of admission, she was found unresponsive in bed by her husband with frothy and blood-tinged saliva and sputum, and incontinence of urine. Physical examination showed an alert and agitated woman. She was afebrile, BP 170/90, HR 120 and RR 20. Neck was supple. There were anterior tongue lacerations and multiple ecchymoses of the right forearm. Neurological examination showed her to oriented to place and time, and she recognized family. She was coherent but inappropriate at times and restless. CT scan of the head revealed a hypodensity in the right frontal lobe, felt to represent an old infarct. The CSF examination was normal. The patient was treated with phenytoin 16 mg/kg IV, diazepam 9 mg IV and midazolam 2 mg IV. For the next 24 hr, the patient remained confused with episodes of agitation and a left-sided hemiparesis with a Babinski sign. An EEG revealed a continuous discharge of focal spike waves recorded from the right frontal region (Fig. 3). At times, the right-sided discharges came close to resembling periodic lateralized epileptiform discharges (PLEDs). An MRI of the head revealed multiple bilateral hyperintense lesions in subcortical and periventricular regions—most likely ischemic in nature. The patient was started on clobazam with a loading dose of 60 mg and a maintenance dose of 20 mg per day, since even with a therapeutic level of 53 μmol/L for phenytoin, she remained agitated and confused. In the next 2 days, the confusion cleared and the patient started to be more oriented without episodes of agitation. The left-sided hemiparesis improved and a repeat EEG revealed no evidence of epileptic activity.

CASE 4

A 49-year-old female presented with a 6-day history of malaise, diplopia, blurred vision and dizziness. Upon admission, she experienced three episodes of generalized tonic-clonic seizures followed by continuous simple partial motor seizures in the right hand and arm. Her past medical history include psoriatic arthritis and non-insulin dependent diabetes mellitus. Examination showed a drowsy woman with recurrent clonic movements of right hand and arm. She

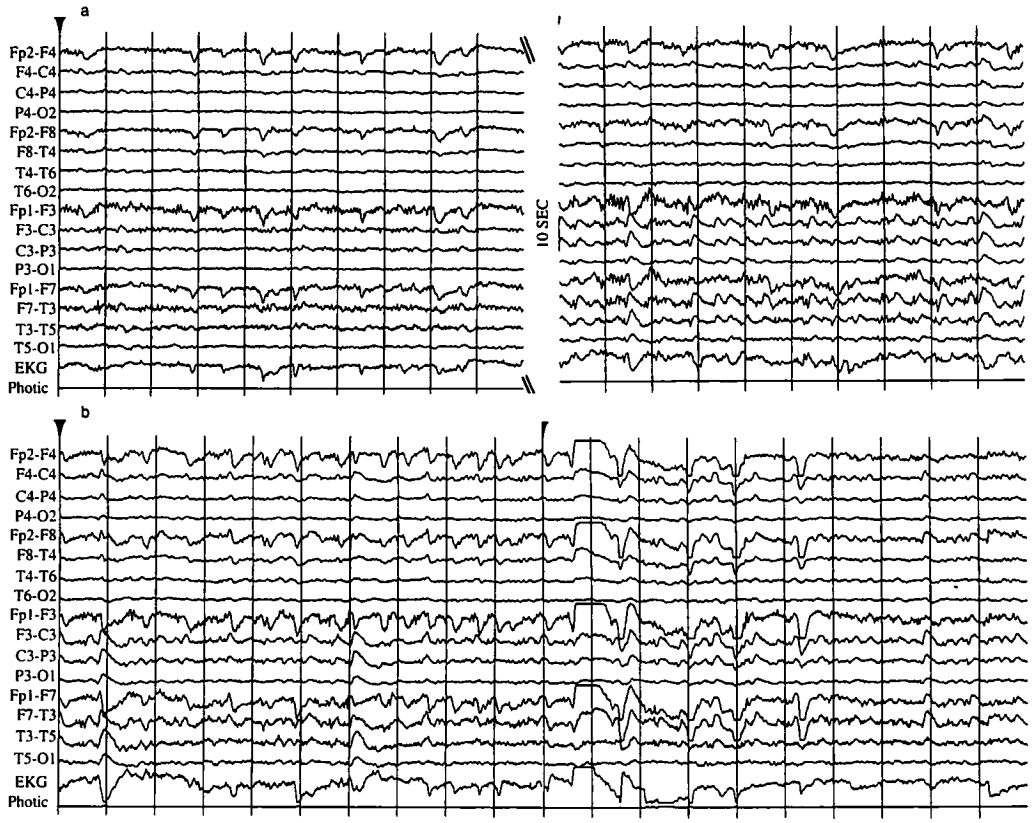

Fig. 1: EEG in Case 1 showing seizure beginning in left frontotemporal area (Fpl-F3 and F7-T3) and lasting approximately 1 min. During this time the patient was motionless and unresponsive.

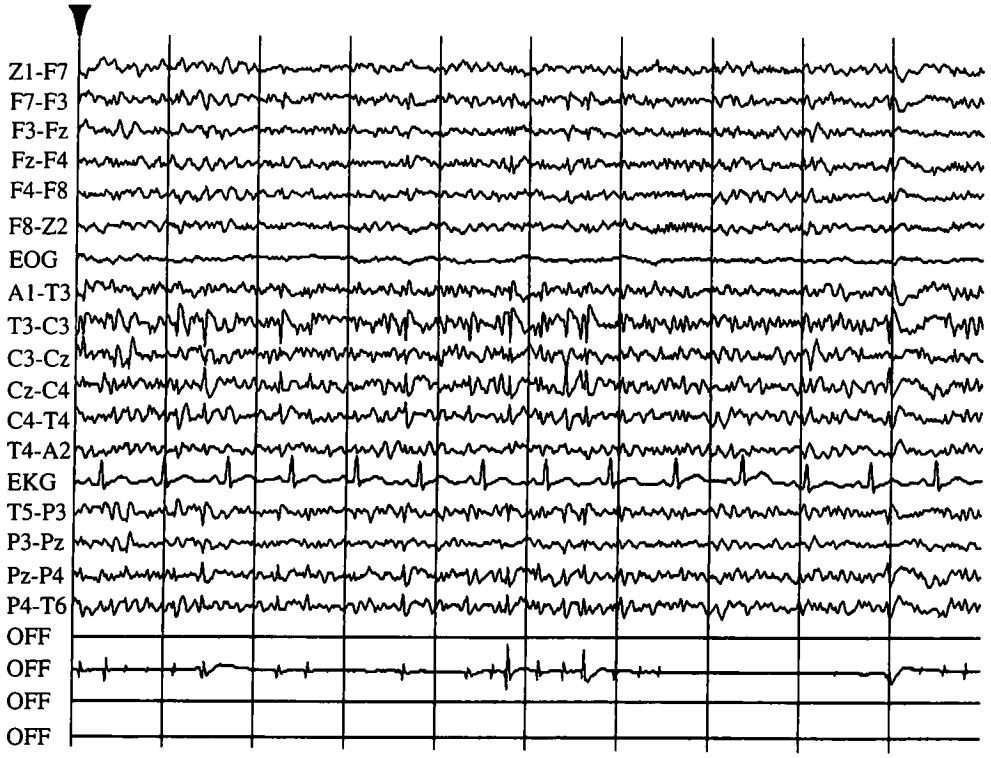

Fig. 2: EEG in Case 2 done during status showing very frequent left central (C3) spikes which were accompanied by right arm twitching.

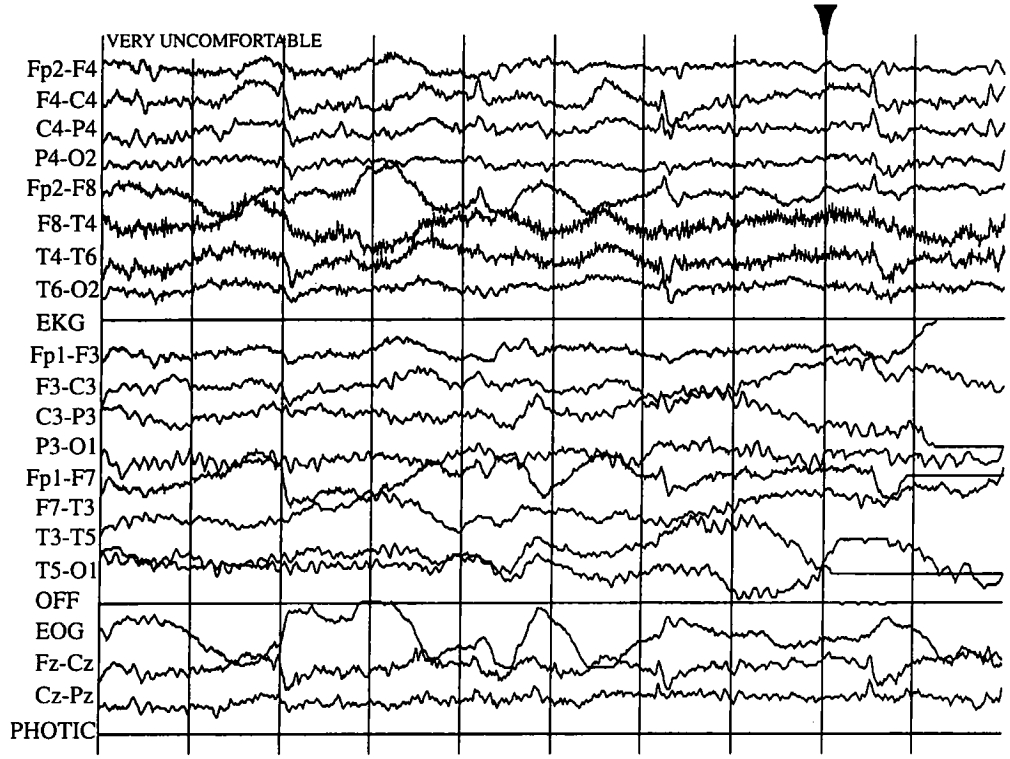

Fig. 3: EEG in Case 3 done during status showing spikes and sharp waves resembling PLEDs recorded from the right fronto-temporal area.

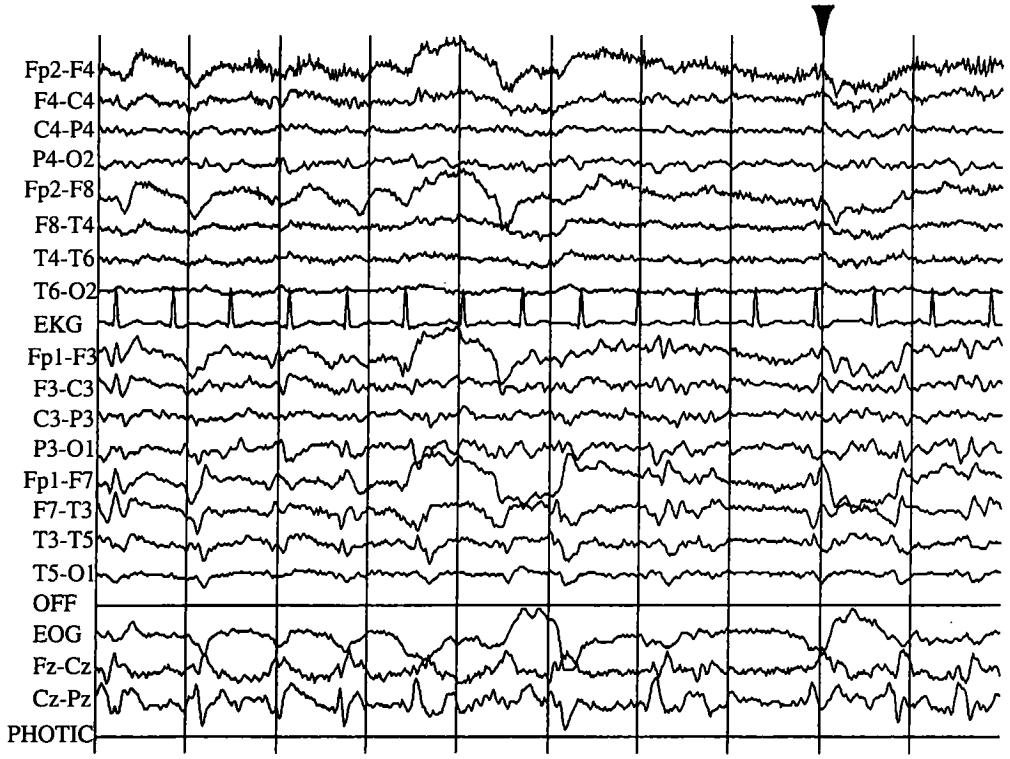

Fig. 4: EEG is Case 4 during status showing left mid-temporal PLEDs extending into central regions.

was febrile and BP100/60. She followed simple commands and answered questions with yes/no. She had a mild right hemiparesis and Babinski sign. CT scan of the head (with and without contrast) and CSF examination were normal. She was initially given only 200 mg phenytoin IV due to hypotension. The patient was subsequently treated with phenytoin 1150 mg IV and lorazepam 3 mg IV. Partial seizures persisted and EEG revealed nearly continuous left midtemporal spike-wave and sharp wave discharges as well as diffuse slowing. The discharges resembled PLEDs at times (Fig. 4). Phenytoin level was 75 μmol/L. Clobazam 70 mg was given orally 16 hr following admission and seizures stopped within 30 min. She became more alert and oriented. An MRI of the head (with and without gadolinium) showed subtle areas of increased intensity on T2-weighted scans affecting left frontal, parietal and temporal areas and possibly the right mesial temporal areas. In addition there were small petechial haemorrhages in the cerebral cortex bilaterally. The diagnosis was felt to be vasculitis, possibly due to lupus but viral encephalitis, possibly due to herpes simplex could not be ruled out. She was treated with corticosteroids, acyclovir and a combination of clobazam (10 mg qam and 20 mg qhs for 4 days then 10 mg twice daily for 3 days then 10 mg per day for 5 days) for 12 days and carbamazepine. Seizures did not recur and a repeat EEG showed only diffuse slowing.

DISCUSSION

Simple partial status epilepticus, especially when it is due to an acute brain lesion, may be resistant to conventional antiepileptic drugs. Complex partial status, although less frequently encountered, may be prolonged and refractory[6,7]. Some of these patients, who have consciousness preserved or lucid intervals between their seizures, are capable of taking oral medication which offers the possibility of early out-patient management. This assumes importance in patients who are subject to recurrent bouts of partial status.

Clobazam has been shown in several European and Canadian studies to be an effective, broad-spectrum antiepileptic add-on agent despite the development of tolerance in approximately half of excellent responders[1,8–10]. There is one report of clobazam administered as a loading dose (0.5 to 1.7 mg/kg, mean 1.08 mg/kg) in 16 patients in status epilepticus. Six were in absence status, one in myoclonic, one in tonic and seven in complex partial status. These authors found that 15 of the patients responded within 25 min of administering clobazam of 6 of these had complex partial status[5].

Our four patients with proven partial status responded promptly to an oral loading of clobazam which was approximately twice the usual daily maintenance dose. An important feature of these cases was that they had already failed to respond to conventional loading doses of phenytoin and lorazepam. The drug was well tolerated and no adverse effects were seen. Patients did not become over-sedated or stuporous following the loading dose.

In conclusion, clobazam given orally in a loading dose in partial status epilepticus is practical and potentially effective. Our experience suggests its efficacy when used following conventional intravenous use of antiepileptic drugs in status. Whether it would be effective as a first-line agent remains to be studied. The pharmacokinetics, including rapid absorption and relatively long half-life, and safety profile of the drug favours its use in these scenarios and further controlled studies are recommended.

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